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08/866,354 05/30/97 FOR A-401B

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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U S PATENT OPERATIONS DRC
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HAYES, R

EXAMINER	
1645	

ART UNIT	PAPER NUMBER
07	[illegible]

DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary

Application No.	Applicant(s)
08/866354	Fox et al.
Examiner	**Group Art Unit**
Vayes	164.5

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Period for Response

A SHORTENED STATUTORY PERIOD FOR RESPONSE IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a response be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for response is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to respond within the set or extended period for response will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☒ Responsive to communication(s) filed on 4/9/98.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle,* 1935 C.D. 1 1; 453 O.G. 213.

Disp sition of Claims

☒ Claim(s) 1-69 is/are pending in the application.

Of the above claim(s) 1-12, 27, 35-52, 59, 61-69 is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 13-26, 28-34, 53-58, 60 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☒ Claim(s) 1-69 are ~~are~~ subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 4

☐ Interview Summary, PTO-413

☒ Notice of References Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other _____

Office Action Summary

DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of Group II in Paper No. 6 is acknowledged. The traversal is on the ground(s) that "the claims are interrelated as evidenced by interdependencies of the claims themselves...", that a "thorough search by the PTO will be based upon both the amino acid and nucleic acid sequences...[and a]s a result, for examination purposes there is no distinction between these entities". Finally, Applicants argue that "because the examination... will involve the same search, there is no serious burden on the examiner...". This is not found persuasive because interrelatedness is not a criteria for defining separable and materially distinct inventions. As previously made of record, each of the products claimed can be prepared by different processes, such as though chemical synthesis or isolation from natural sources using various isolation/ purification procedures, they are physically and functionally distinct, as evidenced by their different classifications, and they can be used in different distinct methods, such as therapeutic agents in gene therapy. Moreover, search of amino acid sequences is but one aspect of a complete search of a protein (i.e., as it relates to Group I), in which the amino acid sequence is only one inherent property of a polypeptide, and does not preclude the existence of the protein prior to knowledge of the gene that encodes it. Nor does the knowledge of a single product preclude using the product in different and materially distinct methods, as previously made of record. It is again pointed out that there is a proper distinction between these groups, since each product is not required in order for the other to exist. Therefore, because these inventions are

distinct for the reasons given above and in the previous Office action, they have acquired a separate status in the art as shown by their different classification, and the non-coextensiveness of the search and examination for each group would constitute an undue burden on the examiner to search and consider each of these separable groups, the requirement is still deemed proper, and is therefore made FINAL.

Claims 1-12, 27, 35-52, 59 & 61-69 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions, the requirement having been traversed in Paper No. 5.

Claim Objections

2. Claims 18, 20, 22-23 & 26 are objected to under 37 CFR 1.75(c) as being in improper form because the claims should refer to other claims in the alternative only. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits.

3. Claims 53-58 & 60 are objected to because it does not comply with 37 C.F.R. § 1.821(d) which requires a reference to a particular sequence identifier (SEQ ID NO:) be made in the specification **and claims** wherever a reference is made to that sequence, versus Figure numbers. See M.P.E.P. 2422.04.

Claim Rejections - 35 USC § 101

4. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 20-22 & 56 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. For example, the current recitation of "A host cell" encompasses a human organism. It is suggested that amending the claims to "an isolated host cell" should obviate this rejection. In particular, amending claim 21 to an "isolated" host cell should be allowable.

Double Patenting

5. Claims 13-26, 28-34 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 13-26, 28-34 of copending Application No. 08/837199. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

6. Claims 13-14, 17-18, 20, 22-26, 28, 31-34, 53-58 & 60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the specific isolated human and rat nucleic acid molecules of SEQ ID NOs. 1, 3, 35, 37, 39 & 41, does not reasonably provide enablement for any nucleic acid sequence comprising a sequence that encodes any biologically

functional equivalent GDNFR protein, or "analog thereof". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The name "nucleic acid encoding a neurotrophic factor receptor" (as it relates to how it is defined on pages 6, 23 & 38-42 of the specification) does not sufficiently characterize and enable the polynucleotides that are encompassed by the claims, because the inclusion of any insertion, substitution and deletion variants thereof, or analogues, homologs, derivatives or fragments thereof, or any biologically functional equivalent protein within the definition of polynucleotides that encode such polypeptides sets forth little structural characterization and little functional characteristics. The general recitation of the name "nucleic acid encoding a GDNFR protein", therefore, encompasses any putative modification, mutation, substitution, addition, deletion, or truncation that results in any nucleic acid encoding a GDNF receptor-related protein (i.e., as it relates especially to claim 13). However, the specification does not teach which particular amino acids are critical for any GDNF receptor protein's function that are encoded by these polynucleotides; nor how to distinguish any "analog thereof" or "hybridization" product of the instant invention from any other nucleic acid molecule that possesses none of the desired functions of the instant invention (i.e., as it relates to claims 13, 14, 17, 28, 31 & 54). Therefore, the skilled artisan would reasonably expect that any such random mutation to a nucleic acid encoding a putative GDNFR-related molecule would result in a polynucleotide encoding an inactive protein. For example, Rudinger states on page 3 that "it is impossible to attach a unique significance to

any residue in a sequence. A given amino acid will not by any means have the same significance in different peptide sequences, or even in different positions of the same sequence". Rudinger further states on page 6 that "the significance of particular amino acid sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study". Therefore, the lack of guidance provided in the specification, as to what minimal structural requirements are necessary for a nucleic acid to encode a functional GDNF receptor protein, would prevent the skilled artisan from determining whether any random modification or mutation to the human or rat GDNF receptor DNA molecules disclosed could be made that retains the desired function of the instant invention, because any such polynucleotide would be expected by to encode proteins that have adversely altered their biologically active 3-dimensional conformation, without undue experimentation to determine otherwise.

Taking this issue one step further, the recitation "*capable* of complexing with... GDNF" encompasses nonfunctional molecules that do not form such "complexes", and hence, a product that does not work. It is suggested that amending claims 17, 28, 53-54 & 60 to minimally require such complex formation with GDNF, as well as amending the claims to more clearly define what "cell response to GDNF" or assayable "GDNF activity" is envisioned to distinguish the nucleic acid molecules of the instant invention from different nucleic acids, which possess none of the desired functions of the instant invention, should obviate these particular components

of this rejection. Alternatively, it would require undue experimentation for the skilled artisan to discover how to make and use Applicants' invention, as currently claimed.

Lastly, in that the claims recite a "nucleic acid sequence encoding a neurotrophic receptor protein", in which the transmembrane domains within SEQ ID NOs: 2 & 4, or Figs. 14-17, are intrinsically embedded within the plasma membrane, the limitation of "secretes said neurotrophic receptor" would not reasonably be expected to occur, as currently claimed (i.e., as it relates to claims 24-25 & 57). Neither would these cells be expected to be "suitable for human transplantation" (i.e., as it relates to isolated non-human host cells), because such cells would elicit an adverse immune response/tissue rejection, and therefore, would not be "suitable for transplantation", by definition. It is suggested that further defining those amino acids truncated to form appropriate soluble receptor molecules, as well as limiting the "suitable cells" to only human cells, provided proper antecedent basis exists within the specification for both amendments, may obviate this particular rejection.

7. Claims 13 & 53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 13 is dependent on nonelected base claims 1-8. Claim 53 is dependent on nonelected base claim 51.

8. Claims 13, 14, 17, 28, 53-54 & 60 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite because it is unclear what metes and bounds are envisioned by the recitations, "mediating cell response to GDNF" and "GDNF activity". It is suggested that amending the claims to a measurable/assayable response due to GDNF binding should obviate this rejection.

9. Claims 17 & 54 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite because it is ambiguous what "but for the degeneracy of the genetic code" means, in regards to whether degeneracy variants of SEQ ID NOs 1 & 3, or sequences in Figs. 19 or 26, are being used as hybridization substrates, or whether degeneracy variants of the hybridization products are being claimed.

10. Claims 22 & 26 are rejected under 35 U.S.C. § 112, second paragraph, for lacking proper antecedent basis for "mammalian cells" and "bacterial cells" (i.e., as it relates to claim 22), as well as for the **cells** intrinsically contained "ex vivo" (i.e., as it relates to claim 26) when "A host **cell**" is claimed.

11. Claims 24, 25, 28 & 57 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite because it is unclear how a cell can "secrete said neurotrophic factor receptor" when the transmembrane domains included within SEQ ID NOs 2 & 4 intrinsically define receptors molecules embedded within a membrane (i.e., as it relates to claims 24, 25 & 57). It is also

unclear what is envisioned by "the step of refolding the isolated neurotrophic receptor", or whether such methods are incomplete, when the neurotrophic receptor intrinsically would already be embedded within a membrane (i.e., as it relates to claim 32).

Conclusion

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Robert Hayes whose telephone number is (703) 305-3132. The examiner can normally be reached on Monday through Thursday, and alternate Fridays, from 8:30 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Paula Hutzell, can be reached on (703) 308-4310. The fax phone number for this Group is (703) 308-0294.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Robert C. Hayes, Ph.D.
July 1, 1998

PAULA K. HUTZELL
SUPERVISORY PATENT EXAMINER